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REVIEW

The Role of Fibroblasts in Atopic Dermatitis: Establishing Proinflammatory Microenvironments and Mediating Cellular Crosstalk

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Abstract: Atopic dermatitis (AD) is a chronic inflammatory dermatosis characterized by skin barrier dysfunction and dysregulation of the immune system. Previous studies have primarily focused on the roles of immune cells and keratinocytes (KCs) in AD. Fibroblasts (FBs) are stromal cells that produce extracellular matrix (ECM) and maintain its homeostasis. However, recent studies indicate that FBs can secrete cytokines and other mediators, thereby actively contributing to immune regulation and the propagation of inflammation. Furthermore, advances in single-cell RNA sequencing and spatial transcriptomics have highlighted the extensive crosstalk involving FBs in AD. In this review, we summarize previously reported evidence regarding the role of FBs in AD to provide a deeper understanding of the pathogenic mechanisms underlying the disease and to suggest new therapeutic for strategies patients, particularly those with inadequate responses to conventional treatments.

Keywords: atopic dermatitis, fibroblasts, extracellular matrix, proinflammatory microenvironment, cellular crosstalk

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Introduction

Atopic dermatitis (AD) is the most prevalent chronic inflammatory dermatosis, characterized by eczematous lesions accompanied by recurrent and persistent pruritus, which significantly impairs patients' quality of life.[1,2] With its increasing prevalence, AD imposes substantial socioeconomic burdens on healthcare systems.[3] Early studies on AD primarily focused on immune dysregulation, particularly the aberrant activation of Th2 cytokines. In 2006, the seminal discovery of filaggrin (FLG) mutations in AD patients led researchers to identify KCs dysfunction and epidermal barrier defects as pivotal pathogenic drivers.[4] Currently, skin barrier disruption and immune dysregulation are the cornerstones of therapeutic strategies targeting AD.[5]

Stromal cells in the skin comprise various cell types, including adipocytes, pericytes, and endothelial cells. Among these, fibroblasts (FBs) constitute the most abundant population and represent the primary source of extracellular matrix (ECM).[6] Studies indicate that in stromal cells, FBs, pericytes and KCs in the stromal cell compartment exhibit the most pronounced inflammatory signatures in AD.[7] The ligands that interacting with Th2 cells and Th22 cells—disease-specific T-cell subsets in AD—are predominantly expressed in stromal cells rather than in inflammatory or immune cells. Notable examples include interleukin (IL)-6, C-X-C motif chemokine ligand 12 (CXCL12), and C-C motif chemokine ligand 2 (CCL2) on FBs as well as IL-18 in KCs.[7] Furthermore, facilitated by advances in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) have enabled researchers to identify distinct pathogenic and pro-inflammatory FB subsets and revealed extensive crosstalk between FBs and various immune cells in AD.[8] These findings underscore the functional heterogeneity of FBs and their active role in inflammatory features not commonly observed in other stromal

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cells.[9,10] Compared with other stromal cells, which may tend to exhibit relatively static and limited functions, FBs display greater heterogeneity, functional diversity, and immunomodulatory capacity.

Current treatment guidelines for AD still leave many patients with inadequate control, highlighting the need for novel therapeutic strategies. A deeper understanding of FB pathophysiology may bridge gaps in our understanding of the pathogenesis of AD and uncover new therapeutic targets.

In this review, we elucidate the extensive interactions between FBs and core AD pathogenic processes in AD, such as the scratch-itch cycle, skin barrier disruption, and aberrant type-2 immune activation. We will also discuss the therapeutic potential of targeting FBs as a promising approach for improving AD management.

Fibroblasts in Skin Barrier Dysfunction

As primary cells of epidermis, KCs proliferation and differentiation are essential for maintaining epidermal homeostasis and skin barriers. Numerous factors, including antigens, cytokines, and transcription factors, intricately participate in the maintenance and regulation of KCs' proliferation and differentiation.[11] Elucidating the specific mechanisms through which these factors influence KCs in the pathological process of AD is essential for understanding this complex disease.

Based on the gene expression patterns, KCs in healthy adult skin can be categorized into four distinct subsets: undifferentiated, differentiated, proliferating, and inflammatory differentiated KCs.[11] There is an increased proportion of differentiated KCs (including inflammatory differentiated KCs), alongside a decreased proportion of undifferentiated and proliferating KCs, indicating an accelerated conversion and differentiation of KCs. Inflammatory differentiated KCs express fewer undifferentiated and differentiated transcripts while also expressing inflammatory transcripts including intercellular adhesion molecule 1 (ICAM1), tumor necrosis factor (TNF) and C-C motif chemokine ligand 20 (CCL20), as well as pro-inflammatory factors such as alarmins (S100A7, S100A8, and S100A9).[12] FBs can regulate these processes through epithelial-mesenchymal transition (EMT) and paracrine signaling thereby affecting the skin barriers of AD (Figure 1).

Epithelial-Mesenchymal Transition (EMT)

EMT is characterized by downregulation of epithelial phenotypes such as E-cadherin and tight junctions and upregulation of mesenchymal markers such as vimentin.[13] EMT can be typically classified as type I occurred in the process of embryonic development, type II in wound healing, fibrosis, and chronic inflammation, and type III in cancer metastasis.[14,15] In Type II EMT, epithelial cells undergoing transition exhibit a fibroblastic phenotype known as FBs or myofibroblasts expressing α-smooth muscle actin (α-SMA). At the same time, these cells secrete pro-inflammatory cytokines and ECM proteins, leading to tissue remodeling. Type II EMT has been proved to be associated with atopic diseases like asthma and allergic rhinitis (AR),[16] though direct evidence linking EMT to AD remains limited.

In AD, type 2 cytokines including IL-4 and IL-13 pronounced in acute stages, and Th1 cytokines like IFN-γ, TNF-α, and transforming growth factor-β (TGF-β) existing in chronic lesions. All these cytokines may collectively drive pathological EMT process.[17] While EMT may facilitate epithelial repair, chronic inflammation-driven excessive EMT promotes morphological alterations in epithelial cells and marked disruption of tight junctions, ultimately compromising skin barrier integrity.[18] One study elucidated that in mouse model, celastrol, the major active component of *Tripterygium wilfordii*—widely used for immunosuppression—can inhibit PKC/Rac1 (Rac Family Small GTPase1) signaling, thereby preventing the topical antigen-elicited upregulation of EMT-related proteins.[19] Another report detailed a young man with anterior subcapsular cataract associated with AD, where researchers found the lens epithelial cells in the cataractous tissue exhibit a myofibroblast phenotype expressing α-SMA, contributing to the deposition of aberrant ECM proteins and the fibrotic response.[20] Kitazawa et al also demonstrated that EMT process in AD was driven by series of transcription factors such as Snai1 and Twist in epithelial cells, and they found reduced E-cadherin and elevated Twist, Snai1, and vimentin expression in both lesional and non-lesional skin of AD patients. Critically, they identified KCs co-expressing the epithelial marker K5 and mesenchymal marker vimentin—evidence of a hybrid epithelial/mesenchymal phenotype—providing a direct pathological evidence for EMT in AD.[21,22]

However, EMT is a double-edged sword and the impairment of EMT will disrupt epithelial homeostasis. Myles et al have demonstrated that sphingolipid production by *Roseomonas mucosa* (R. mucosa) activates nAChR (nicotinic

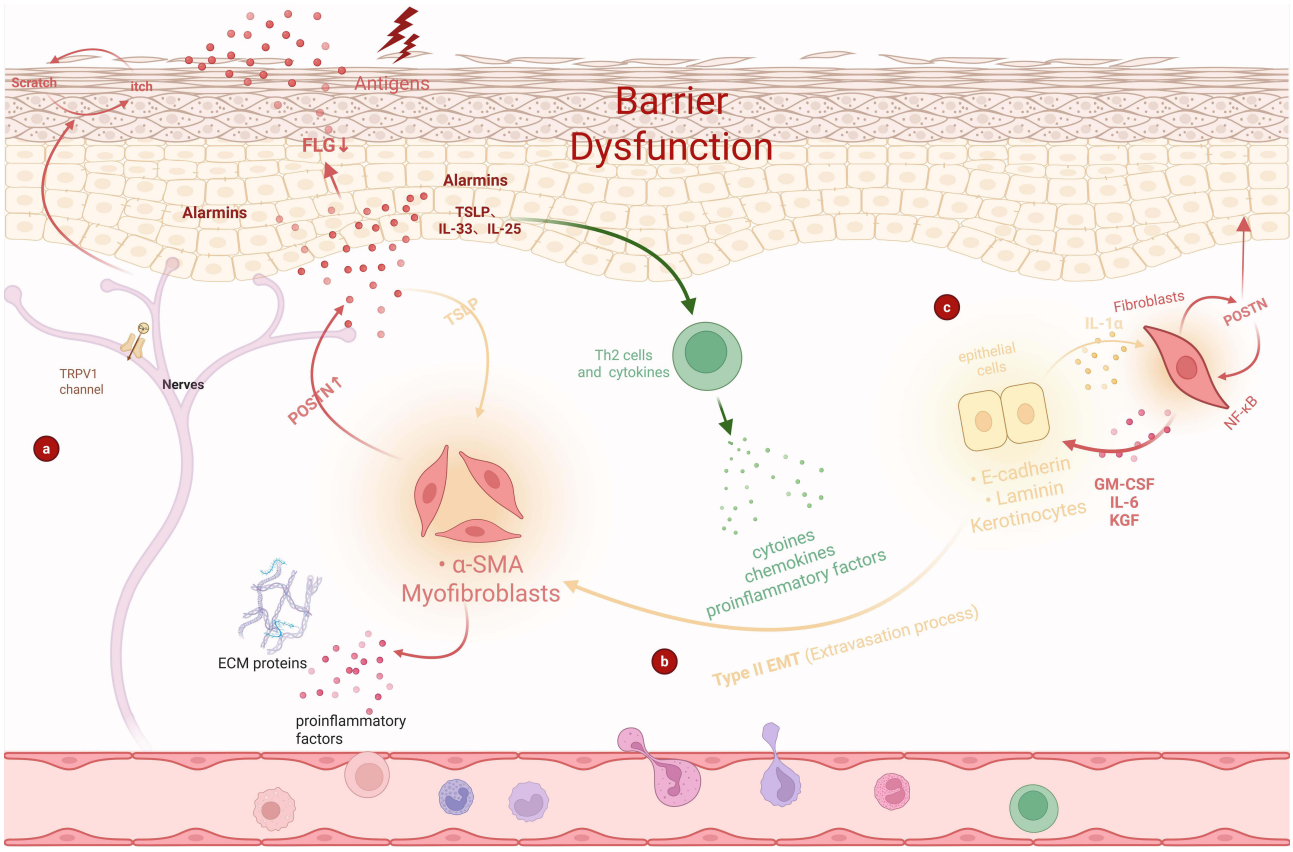

Figure 1 A schematic overview of FBs role in dermal-epidermal crosstalk and pruritus. (**a**) TSLP can act on sensory neurons and induce pruritus. FBs secrete POSTN to stimulate KCs, which in turn release TSLP, amplifying pruritus. (**b**) Inflammatory mediators such as cytokines and chemokines drive the induction of EMT. Myofibroblasts can produce ECM-associated proteins and pro-inflammatory factors. (**c**) The POSTN autocrine loop and the IL-6/IL-1α paracrine loop represent key mechanisms by which FBs regulate proliferation and differentiation of KCs. (Image created with Biorender.com.).
Abbreviations: TSLP, Thymic stromal lymphopoietin; POSTN, Periostin; FBs, Fibroblasts; KCs, Keratinocytes; EMT, Epithelial-mesenchymal transition.

acetylcholine receptor) and TLR5 (Toll-like receptor 5) signaling, thereby inducing TNFR2 (tumor necrosis factor receptor 2)-mediated EMT.[23] This process promotes epithelial regeneration and restores functional skin barrier integrity. Topical nAChR-targeting agents such as tapinarof,[24] alongside probiotic interventions that reconstitute commensal microbiota, represent promising therapeutic targets for AD through EMT restoration and subsequent barrier recovery.

The Paracrine Signaling of Fibroblasts Directs Keratinocytes Behavior

In vitro studies indicate that extracting cell culture medium from atopic-like skin models and applying it to normal bronchial epithelial models result in an inflammatory phenotype. Proteomic analysis reveals that the primary components of the cell culture medium are ECM-associated proteins, likely secreted by abnormal pro-inflammatory FBs subsets, such as the COL6A5+COL18A1+FBs subpopulation.[8] This suggests that FBs involved in skin ECM remodeling play a critical role in skin-lung epithelial cells axis in atopic march.[25]

Recognizing the importance of FBs-KCs interactions in skin physiology,[26] researchers have established a three-dimensional skin equivalent using ECM derived from FBs and primary KCs. This skin model exhibits enhanced barrier function (characterized by a fully differentiated and cornified epidermis, a more stable dermal-epidermal junction, and reduced skin permeability), and the balance in Ras/Raf/ERK/MEK signaling pathway[27] than monolayer cell cultures, such as traditional HaCaT cells.[28]

Numerous studies run parallel to the aforementioned researches. FBs from AD patients can disrupt the differentiation-associated leukemia inhibitory factor (LIF)-signal transducer and activator of transcription 3 (STAT3) signaling pathway, thereby reducing FLG expression. Recent findings suggest that loss-of-function mutations in the FLG gene represent the

most significant genetic risk factor for AD.[29] Thus, we can conclude that the reduction in FLG levels results not only from FLG mutations but also from the skin microenvironment, which is influenced by FBs and ECM. FBs induce dysfunction of epidermal-dermal crosstalk within skin equivalents, independent of FLG mutations, leading to epidermal thickening, parakeratosis, and hyperproliferation. Furthermore, the skin equivalents exhibit a FLG-deficient phenotype characterized by elevated TSLP levels, which recruit the CD4+T cells to the dermal stratum and promote the secretion of type-2 cytokines such as IL-13.[30] In contrast, FBs from healthy individuals can restore the normal structure of epithelial cells, partly due to LIF derived from FBs.[31]

FBs primarily regulate KCs proliferation and differentiation in a paracrine manner. These processes can be modulated by various soluble factors, such as IL-1 and IL-6, growth factors including GM-CSF and fibroblast growth factor,[32,33] and other secreted factors such as stromal cell-derived factor 1 and pleiotrophin. KCs constitutively express IL-1α, inducing FBs to secrete IL-6—a key regulator of KCs proliferation and differentiation. This establishes an IL-1α/IL-6 paracrine axis. Concurrently, FB-derived periostin (POSTN) activates NF-κB signaling, synergizing with IL-1α to amplify IL-6 production. This POSTN-dependent autocrine loop spatiotemporally enhances IL-6 expression, promoting KCs and FBs proliferation/differentiation to accelerate wound healing.[34,35] As a critical component of ECM proteins, POSTN plays a critical role in epithelial-mesenchymal interactions and inflammation in AD. It is increasingly recognized that a complex regulatory network governs epithelial-mesenchymal crosstalk, characterized by a double paracrine loop involving IL-1α and IL-1β produced by KCs and KGF or GM-CSF secreted by FBs.[32,33]

Gaspar et al demonstrated significantly elevated CCR3 (C-C Chemokine Receptor 3) expression on FBs in AD patients. CCR3-CCL26 interaction drives skin remodeling. In AD, KCs are the dominant source of CCL26 and eosinophils (EOS) represent another significant contributor to CCL26 production.[36] Additionally, these interactions could serve as biomarkers for the treatment of dupilumab. Reductions in CCL26 had the highest correlation with improvement in percentage change in the EASI score.[37]

Fibroblasts in Pruritus of AD: Functioning as Amplifiers

Accompanied by scratching behaviors, pruritus exacerbates skin barrier damage and leads to the secretion of downstream factors known as alarmins. Recent researches have elucidated that the pathogenesis of the pruritus in AD, identifying various contributing factors, including environment factors, pruritus-associated cytokines such as IL-33, TSLP, and histamine, skin barrier dysfunction, and nerve sensitization.[38–40] FBs can mediate pruritus through cellular interactions and the secretion of pruritogens via a paracrine mechanism.

Crosstalk Between Fibroblasts and Neurons

In AD, epidermal nerve density is increased, resulting in abnormal pruritus perception, which is partially regulated by KC-derived nerve growth factor (NGF).[41] Murota et al has demonstrated that FBs-derived artemin, a member of glial cell line-derived neurotrophic factors (GDNFs), when stimulated by substance P, can also induce abnormal proliferation of peripheral nerves when stimulated by substance P, thereby leading to warmth-related pruritus in AD.[42] FBs lacking Ikk2, which mediates the activation of NF-κB, exhibit pruritus independent of TSLP and transit receptor potential ankyrin1-expressing nerves (TRPA1)-expressing nerves.[43]

Fibroblast-Derived Pruritogens: POSTN

POSTN act as a bridge between type-2 inflammation and FB-associated pruritus through paracrine signaling. High-mobility group box 1 protein (HMGB1) can bind to TLR4 on FBs as an alarmin,[44] activating NF-κB/p65 signaling to induce the release of pruritogens IL-33 and POSTN—key mediators in FB-associated pruritus.[45] Stimulated by type-2 inflammatory cytokines, FBs will produce POSTN,[46] which can directly induce pruritus by activating peripheral sensory neurons, such as dorsal root ganglia (DRG) neurons, and promoting the opening of calcium-permeable ion channels, including transit receptor potential vanilloid 1 (TRPV1) or TRPA1.[47]

Furthermore, through cellular crosstalk among FBs, KCs, and immune cells, POSTN can evoke a series of pruritogens including TSLP.[46,48] KCs can be induced to produce TSLP, while TSLP binding to its receptor on KCs activates a reciprocal amplification loop involving TSLP and POSTN, with FBs-derived POSTN serving as an initiator.[46]

Fibroblasts and Immune System

Crosstalk Between Fibroblasts, Eosinophils, and Basophils

Pathological EOS, served as the primary effector cells in AD lesions, are capable of producing numerous toxic granule proteins and lipid mediators locally,[49] thereby leading to tissue injury and dysfunction. These processes, including trafficking, primarily mediated by EOS chemoattractants such as IL-5 and CCL11 (eotaxin-1),[50] as well as adhesion, activation, and the release of cytotoxic proteins,[51] transform normal EOS into a pathogenic phenotype and extensively infiltrate into AD skin lesions.[52]

In AD lesional skin, EOS must navigate through the EOS-endothelial adhesion via VCAM-1 (vascular cell adhesion molecule-1), transendothelial migration, and migration across the FBs with β2-integrins and their receptors such as ICAM-1,[53] ultimately leading to extensive infiltration at the dermal-epithelial junction.[54] FBs, as stomal cells, are significantly involved in these processes, aided by macrophage migration inhibitory factor (MIF).[55] Stimulated by type-2 inflammatory factors such as TNF-α, IL-4, IL-33, and IL-31,[56,57] FBs can produce CCL11 at levels several times higher than those of normal FBs. This finding indicates that FBs, as downstream effectors of type-2 inflammation in the co-culture systems, play a critical role in exacerbating the type-2 inflammation cascades.[58,59] Blocking Ikkβ (inhibitor of nuclear factor κB kinase subunit) in paired related homeobox-1-positive FBs (Prx1+FBs) leads to the upregulation of CCL11 and disrupts normal skin homeostasis, thereby causing EOS infiltration and contributing to AD lesions.[60]

A study by Gahr et al has demonstrated that IL-4-induced CCL11 mRNA expression in FBs exhibits heterogeneity and variability among different populations and stages of AD, with the most pronounced effects observed in acute AD.[61] Concurrently, type-2 inflammatory factors can also differentially up-regulate ICAM-1 and VCAM-1 expression on human lung FBs. This evidence highlights association of FBs with the heterogeneity of AD.

Researchers have found that the crosstalk among FBs, EOS, and basophils is bidirectional in co-cultivation systems in vitro. The communication between FBs and EOS is mediated solely by soluble mediators, contrasting with the direct cell-cell contact observed between FBs and basophils. In co-culture systems, EOS and basophils produce several times larger amounts of inflammatory cytokines and chemokines; conversely, FBs also produce more CCL11 compared to mono-systems.[56,59] FBs activated by *Staphylococcus aureus* (*S. aureus*), in combination with NOD2 (*S. aureus*-associated nucleotide-binding oligomerization domain-containing protein2) and TLR2 (toll-like receptor2) through P38-MAPK, NF-κB, and ERK signaling pathways, subsequently induce pro-inflammatory cytokines derived from EOS and basophils.[62] Additionally, EOS degranulation products can upregulate the expression of IL-6 and IL-8 in FBs, thereby amplifying neutrophils migration.[63]

Crosstalk Networks Among Fibroblasts, Macrophages, Dendritic Cells and T Cells

Spatial transcriptomics, proteomics, and single-cell RNA sequencing technologies have advanced research on AD into a micro-scale domain, focusing on molecular changes at the single-cell level rather than relying on whole tissue biopsies as in previous studies. Concurrently, researchers have developed various painless sampling methods, such as tape stripping, skin suction blistering,[64] saline wash samples,[65] and the analysis of peripheral mononuclear blood cells (PMBCs),[66] to obtain more samples and broaden the scope of research.

By applying single-cell RNA sequencing to biopsy specimens of AD patients, novel inflammatory subsets of FBs, specifically COL6A5+COL18A1+FBs, have been identified. COL6A5+COL18A1+FBs are exclusively found in AD lesional skin, while MFAP5+FBN11+FBs are present in both healthy and lesional skin in AD. Activated FBs in AD skin significantly upregulate the expression of pro-inflammatory cytokines, chemokines, and ECM-associated proteins (including POSTN, TNC, and VCAM-1). Activated COL6A5+COL18A1+FBs can secrete pro-inflammatory cytokines such as CCL2, CCL19, and IL-32.[8,64] Furthermore, these cells are localized specifically at the dermal-epidermal junction within leukocyte-infiltrated area, while COL18A1+FBs are distributed throughout the dermis.

Widespread co-localization and interactions are observed among COL18A1+FBs, M2 macrophages expressing CCL13, CCL18, CCR1, and CCR2 specialized inflammatory dendritic cells[67] expressing CCR7 and LAMP3, and T cells expressing CD3 and CCR7.[8,64] CCR7 is mainly expressed in T cells and DCs (the receptor of CCL19),[7,64] indicating the role of FBs in the recruitment and polarization of T cells. Some of the secretions from these cells, including

CCL18,[7] tenascin-C (TNC), and regenerating islet-derived protein 1 alpha (REG1A), correlate with serum levels and are closely associated with scoring atopic dermatitis (SCORAD) as potential biomarkers.[64] These cell-cell interactions create a localized inflammatory microenvironment and contribute to broader immune system responses by releasing soluble factors, ultimately leading to systemic inflammation in AD.

Cellular interactions among KCs, FBs, and mast cells promote the development of AD, mediated by a series of soluble factors. HDAC6 (histone deacetylase 6) and CXCL13 (CXC chemokine ligand-13) have been shown to be one of the soluble mediators in these cellular communications in mouse model.[68] HDAC6 inhibitors tubastatin A and belinostat can restore epidermal differentiation thereby ameliorating skin barrier defects.[68,69]

The Proinflammatory Microenvironment: A Synergistic Nexus of Extracellular Matrix Remodeling and Immune System Activation

ECM is mainly composed of macromolecular components, and its precise composition shows dynamic heterogeneity. Through proteomics and in-silico approaches, explorers define ECM-matrisome gene sets such as COL1A1 and COL5A1, as well as cell surface receptors CD34 and PDGFRA (platelet-derived growth factor receptor alpha) as the predominant driver of FBs heterogeneity.[70] The tissue microenvironment affects functional states of local immune cells, with tissue-resident FBs emerging as pivotal regulators of immune activation versus suppression.[71] Traditionally, the ECM has been recognized for maintaining skin structural integrity through biomechanical cues and providing physical support to cells.[72] Emerging evidence indicates active crosstalk between ECM components and receptors on the cell surface (eg, CD44 on leukocytes), regulating cellular proliferation, differentiation, and inflammatory processes to orchestrate tissue homeostasis.[73]

As previously discussed, TGF-β serves as a pivotal mediator in immune-ECM interactions by promoting myofibroblast differentiation, collagen production, and the suppression of matrix-degrading metalloproteinases.[74,75] Furthermore, type 2 immune responses are closely linked to ECM remodeling, with type 2 cytokines such as IL-13 directly modulating ECM structure and function.[76] Similarly, hyaluronan (HA) within the ECM binds to CD44 on leukocytes, facilitating leukocyte migration and recruitment during inflammation. Conversely, leukocytes regulate HA via CD44-mediated uptake and degradation.[77]

The role of ECM remodeling in AD remains underexplored. Studies suggest that ECM-associated proteins—including collagen subtypes, keratins, laminins, fibronectin (FN), thrombospondin-1 (TSP-1), complement component 3 (C3), CD44, and syndecan-4 (SD-4)—may trigger bronchial epithelial inflammation in AD-like skin models.[25] These mediators induce CD4+ T-cell polarization at the transcriptional level.[78]

FBs derived from AD patients exhibit distinct ECM profiles under in vitro stimulation compared to healthy controls, characterized by disorganized collagen bundles and reduced matrix density. Semi-quantitative proteomic analysis reveals decreased expression of classical ECM proteins (eg, collagen, tenascin, and fibronectin) and upregulated proinflammatory mediators such as serine protease HTRA1 and FB-associated signaling proteins. FBs also contribute to inter-tissue communication, where ECM remodeling-driven skin-lung epithelial crosstalk may underlie atopic march process.[25] Transcriptomic alterations in FBs associated with ECM degradation and remodeling suggest that certain proinflammatory FBs may directly drive pathological ECM changes. For example, COL6A5+FBs can cause abnormal FB adhesion, collagen synthesis, and metabolism, as well as barrier dysfunction through the production of unstable heterotrimers.[8,79]

FB-derived ECM creates a normal microenvironment that can counteract maladaptive pressure on macrophages[80] and other immune cells such as EOS, thus contributing to a reduction in inflammation in AD. Macrophages alter their transcriptome to adapt to the surroundings, acquiring various functions, such as macrophage-myofibroblast transition in fibrotic disease progression,[81] a phenomenon known as macrophages plasticity.[82] Recent researches have demonstrated FB-derived ECM can intervene in the differentiation of macrophage into resident S1 subsets (FRβ/CD163+), contributing to skin homeostasis through efferocytosis and the regeneration of monocytes and EOS, along with chemokine production.[83] FRβ+ macrophages will gain the CD163+ phenotype to become the S1 subset only when exposed to FB-derived laminin-α2 and type-V collagen. Furthermore, laminin-α2 can also reprogram EOS to adopt a non-pathological phenotype, restoring the expression of protease-activated receptor-3 (PAR3) through FB-S1 macrophage crosstalk (Figure 2).[52]

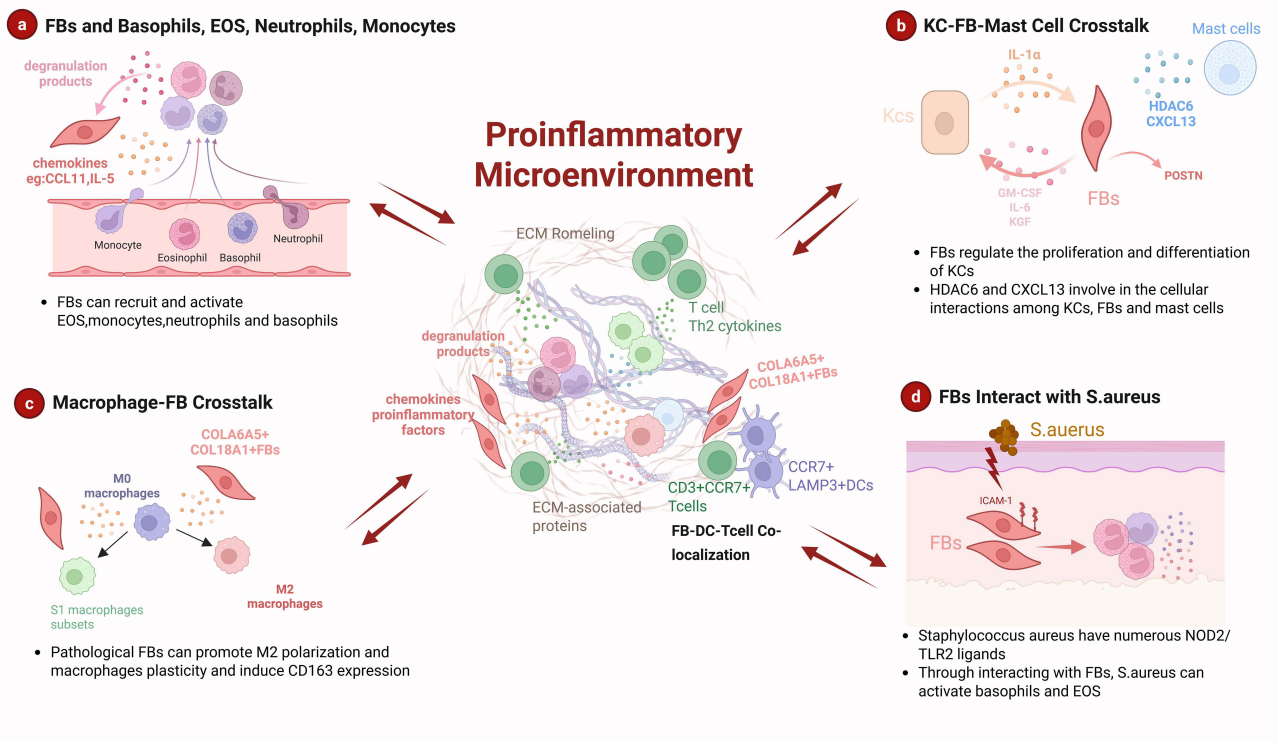

Figure 2 A schematic overview of the reciprocal interactions between the pro-inflammatory microenvironment and immune cells, which can be regarded as a pathological unit of AD. Various cellular components such as immune cells and KCs contribute to the activation of pathogenic FBs subsets and ECM remodeling. Simultaneously, the remodeled ECM displays enhanced pro-inflammatory capacity, creating a vicious cycle that perpetuates inflammation. Spatial transcriptomic analyses of AD lesional skin in AD have revealed co-localization of multiple cell types such as CD3+CCR7+ T cells, CCR7+LAMP3+ DCs, and COL6A5+COL18A1+FBs, suggesting functional crosstalk among these populations. Targeting disease-specific FBs subsets may represent a promising therapeutic strategy for AD. (**a**) Pathological FBs can recruit and activate immune cells through the secretion of various cytokines. In turn, mediators released upon immune cell degranulation will further activate these FBs. (**b**) IL-1α derived from KCs and IL-6 produced by FBs mediate the interactions between FBs and KCs, which mast cells also participate in through HDAC6 and CXCL13. (**c**) Pathological FBs contribute to macrophage plasticity by inducing the differentiation of S1 (FRβ/CD163+) and M2 subsets. (**d**) Beyond their interactions with immune cells in AD, FBs also play a role in the pathogenicity of *S. aureus*. Through NOD2/TLR2 ligands, FBs can activate EOS and basophils, culminating in a cascade of skin damage. (Image created with Biorender.com.).
Abbreviations: AD, Atopic Dermatitis; FBs, Fibroblasts; KCs, Keratinocytes; ECM, Extracellular Matrix; DCs, Dendritic Cells; HDAC6, Histone Deacetylase 6; CXCL13, CXC Chemokine Ligand-13; NOD2, Nucleotide-binding Oligomerization Domain-containing Protein 2; TLR2, Toll-like Receptor 2; EOS, Eosinophils; S. aureus, Staphylococcus aureus.

FBs are the most evidently aging cells in the skin of elderly AD patients,[84] and FBs-related genes are upregulated in the elderly population.[85] Senescent FBs can upregulate the expression of FB-specific senescence-associated secretory phenotype (SASP)-related genes, such as chemokine CXCL1, CCL2, and cytokines CSF1 and IL-6, as well as proteases matrix metalloproteinases (MMPs) like MMP14 and MMP19.[86] These upregulated pathways contribute to ECM structural disruption, skin senescence, the establishment of a chronic inflammatory microenvironment. Senescent FBs also decrease the production of IGF-1, which is necessary for KC differentiation, disrupting the normal dermal-epidermal interactions.[87] In turn, this context enhances the ability of FBs to recruit and activate innate immune cells, such as NK cells, macrophages, and neutrophils in skin. The microenvironment established by senescent FBs plays a key role in the pathogenesis and phenotypic variation of elderly AD, which causes the dysfunction of innate immune system and over-expression of SASP.[88]

Fibroblast-Targeted Therapies in Atopic Dermatitis

In recent years, there has been a growing body of literature focused on immune-targeted biologics for AD, particularly those specifically targeting type-2 cytokines. Dupilumab is one of the most representative biological agents for AD, selectively inhibiting type-2 inflammation through IL-4Rα blockade.[89] This mechanism may partially influence the behaviors of FBs through unidirectional inhibition of cellular crosstalk between FBs and the immune system.

Healthy FBs maintain tissue homeostasis through structured ECM remodeling and reparative functions. In vivo and vitro models demonstrate that HDFn-Ex (exosomes stemmed from human neonatal dermal fibroblasts) can downregulate

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skin barrier-related proteins such as filaggrin, involucrin, and loricrin,[90] while upregulating PPAPα (peroxisome proliferator-activated receptors-α) in KCs,[91] thereby suppressing hyperkeratosis and restoring skin barrier function in AD. Mesenchymal stem cells (MSCs) and their derivatives enhance KCs and normal FBs proliferation primarily through growth factors like vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF). Furthermore, MSCs can differentiate into FBs and secrete barrier-repair cytokines, offering potential therapeutic avenues for AD.[92]

Current FB-targeted therapeutic strategies predominantly focus on inhibiting the process of proliferation, differentiation, and activation in special FBs subpopulations associated with disease pathology. For example, fibroblast activation protein (FAP) inhibitors targeted FAP, a marker of the activation of cancer-associated fibroblasts (CAFs) and FBs in the lungs, thereby impeding tumor progression and the pathogenesis of interstitial lung disease.[93,94] Similarly, Notch-signaling blockade via monoclonal antibodies specifically inhibits CD90 (THY1+) FBs in rheumatoid arthritis.[74] These collective findings underscore the necessity for precise delineation of pathogenic FB subsets and their activation-specific molecular signatures to advance the precision of fibroblast-targeted therapies. In AD, tacrolimus, which suppresses TGF-β1-mediated (transforming growth factor beta 1) activation of FBs, reversing the downregulation of MMP-1 and type I collagen.[95] Additionally, nemolizumab, targeting IL-31 signaling, contributes to pruritus relief, partially through suppression of FBs activation.[96] However, these pharmacological agents achieve only partial blockade of FBs activation, and AD-specific subsets and their definitive pathogenic signatures have not yet been clearly elucidated.

Notably, studies reveal that some subsets of FBs possess innate immune-like memory-like responses to pathogenic stimuli.[97,98] This acquired memory phenotype may contribute to therapeutic resistance in chronic AD.[99] FBs exhibit marked functional and transcriptional heterogeneity. Moreover, diverse pathogenic cytokine profiles and extensive cellular crosstalk involving FBs present challenges for precision FB-targeted therapies. For example, some broad-spectrum anti-inflammatory targets, such as IRAK4, a kinase that acts at the interface between innate and adaptive immune responses, exert limited effects on dermal FB responses despite systemic suppression of immune cells.[100]

Fully realizing FB-targeted strategies for AD requires comprehensive mapping of FB-associated crosstalk networks, and elucidating FB interactions with pro-inflammatory mediators. Addressing these gaps will unlock novel therapeutic paradigms for AD management.

Conclusion

Recent studies have increasingly highlighted the pivotal role of FBs in non-fibrotic autoimmune skin diseases. Pathological FBs have been identified as critical amplifiers of AD inflammation through extensive crosstalk networks with KCs and immune cells. Beyond their traditional role of synthesizing the ECM, FBs can also directly engage in the pathogenesis of AD via paracrine signaling and other immune-like mechanisms. The extensive crosstalk capability of FBs enables them to amplify inflammatory responses, and the potential conservation of specific underlying pathways positions them feasible therapeutic targets. However, research on FBs remains limited, likely due to an incomplete understanding of their upstream regulatory mechanisms. As an emerging focus in AD pathogenesis, targeting FBs holds promise for patients with inadequate responses to current guideline-based therapies. Moreover, the extensive crosstalk of FBs offers multiple potential nodes for combination therapeutic approaches. In summary, FBs represent a promising therapeutic target, paving the way for new directions in the management of AD.

Abbreviations

α-SMA, α-smooth muscle actin; AD, Atopic dermatitis; C3, complement component 3; CAFs, cancer-associated fibroblasts; CCL2, C-C motif chemokine ligand 2; CCR3, C-C Chemokine Receptor 3; CXCL12, C-X-C motif chemokine ligand 12; CXCL13, CXC chemokine ligand-13; ECM, Extracellular matrix; EMT, Epithelial-Mesenchymal Transition; EOS, Eosinophils; FAP, fibroblast activation protein; FBs, Fibroblasts; FLG, filaggrin; FN, fibronectin; GDNFs, glial cell line-derived neurotrophic factors; HA, hyaluronan; HDAC6, histone deacetylase 6; HDFn-Ex, exosomes stemmed from human neonatal dermal fibroblasts; HGF, hepatocyte growth factor; HMGB1, High-mobility group box 1 protein; ICAM1, Intercellular Adhesion Molecule 1; Ikkβ, inhibitor of Nuclear factor κB kinase subunit; IL, Interleukin; KCs, Keratinocytes; LIF, leukemia inhibitory factor; MIF, macrophage migration inhibitory factor; MMPs,

matrix metalloproteinases; MSCs, Mesenchymal stem cells; nAChR, nicotinic acetylcholine receptor; NOD2, *S. aureus*-associated nucleotide-binding oligomerization domain-containing protein2; PAR3, protease-activated receptor-3; PDGFRA, Platelet-Derived Growth Factor Receptor Alpha; PMBCs, peripheral mononuclear blood cells; POSTN, periostin; PPAPα, peroxisome proliferator-activated receptors-α; Prx1, paired related homeobox-1-positive FBs; Rac1, Rac Family Small GTPase1; REG1A, regenerating islet-derived protein 1 alpha; SASP, senescence-associated secretory phenotype; SCORAD, scoring atopic dermatitis; scRNA-seq, single-cell RNA sequencing; SD-4, syndecan-4; STAT3, signal transducer and activator of transcription 3; ST, spatial transcriptomics; TGF-β, transforming growth factor-β; TGF-β1, transforming growth factor beta 1; TLR2, toll-like receptor2; TLR5, Toll-like receptor 5; TNC, tenascin-C; TNFR2, tumor necrosis factor receptor 2; TRPA1, transit receptor potential ankyrin1-expressing nerves; TSP-1, thrombospondin-1; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

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We declare that the paper has not been submitted to another journal, and it has not been published in whole or in part elsewhere previously.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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